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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,728	12/28/2000	Akihiro Umezawa	766.43	6784

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,728	UMEZAWA ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-63 and 78-91* is/are pending in the application.

4a) Of the above claim(s) *47-63 and 78-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-1-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-27-04 has been entered.

2. Claims 47-63 and 78-91 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 17.

3. This application contains claims 47-63 and 78-91, drawn to an invention nonelected with traverse in Paper No. 17. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Claims 1 and 6-46 are under consideration.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 and 6-24, 26-39, 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) an isolated mouse stem cells isolated from an adult mouse bone marrow, wherein said mouse stem cell differentiates into a cadiomyocyte in the presence of a factor selected from the group consisting of 5-azacytidine, DMSO, PDGF, FGF-8, retinoic acid, ET-1, midkine, BMP4, NKX2.5/CSX and GATA4, and wherein said stem cell when transplanted in a

mouse differentiates into cardiomyocyte or wherein said stem cell when transplanted into a mouse blastocyst differentiates into a cardiomyocyte, does not reasonably provide enablement for any other claimed embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention as instantly presented encompasses an isolated multipotential stem cell from any organism, wherein the stem cell can differentiate into each of a cardiomyocyte, an adipocyte, a skeletal muscle cell, an osteoblast, and a vascular endothelial cell. Dependent claims recite that the stem cell can differentiate any cell or is positive or negative for certain markers, or is obtained by treating cells by certain factors or the stem cell is derived any mammal including a

mouse, rat, pig, hamster, rabbit, cat, dog, sheep, swine, cattle, goat or human. Claims 40 and 41 recite intended use of transplantation into a heart or a blastocyst.

The specification as filed teaches culturing mouse bone marrow cells to obtain immortalized mesenchymal cells which when treated with 5-azacytidine for 24 hours differentiate into cardiomyocytes (see example 1). Examples 2-11 disclose characterization of the cardiomyocytes differentiated from the stem cells. Example 12 teaches that BMSCs that differentiate into expressed PPAR-gamma1 was expressed but PPAR-gamma2 was not expressed in these cells. Treatment of these cells with PPAR-gamma agonists resulted into differentiation into adipocytes, however, the example does not provide any evidence whether the differentiated cells functioned as adipocytes. Similarly, while the scpecification using a chimeric transgenic mouse model, discloses that GFP expression from BMSCs that lodged into liver and brain, there was no evidence whether these cells functioned as a brain cell or a liver cell (see example 13). The specification does not teach characterization of the lodged cells as brain cell or liver cell. It is noted that while the claims recite any vitamine, cytokine, growth factor or transcription factor for differentiating into a cardiomyocyte, the only factor which caused differentiation of the bone marrow stem cells to cardiomyocytes was 5-azacytidine whereas DMSO, PDGF, FGF-8, retinoic acid, ET-1, midkine, BMP4, NKX2.5/CSX and GATA4 caused the differentiation of only 50% of the cells into cardiomyocytes. The specification does not provide any guidance or any evidence that any cytokine, growth factor, vitamin, transcription factor or DNA demethylation agent caused differentiation of bone marrow stem cells into cardiomyocytes or any other cell type.

At the time of the invention, the art of a multipotent stem cell from adult bone marrow was unpredictable. For example, Ho et al (Journal of Leukocyte Biology 73:547-555, 2003) reviewed the state of the art of adult stem cells differentiating into different cell types and noted that the validity and interpretation of initial data of the plasticity potential of somatic stem cells (see the abstract). The authors further noted, "Reports of successful expansion of HSC derived from adults in the laboratory have thus far been controversial and have yet to be reproduced." It is noted that this shows that even the expansion of hematopoietic stem cells

from adult bone marrow of human subjects was unpredictable and there was no evidence that any other cell type could be differentiated from adult human bone marrow stem cells. The authors further discussed "In vivo and in vitro studies have shown that marrow derived MSC were able to differentiate into adipocytes, cartilage, bone, tendon, vascular smooth muscle [36-38], cardiac muscle [39], and lung [40]. It remains debatable whether one single-cell type between MSC or HSC is responsible for the plasticity or transdifferentiation potential of BM cells or whether different subsets, each having completely transdifferentiation potentials, are present. Although these issues will probably remain controversial for the next few years, there is nevertheless evidence that pluripotent population(s), it at all, are derived from hematopoietic tissue, i.e. the BM" (see the last paragraph in the right column on page 548 continued in the left column on page 549). The unpredictable nature of the art is further discussed by the authors by discussing controversial results by Krause et al and Wagers et al, whose results were opposite of each other. One reported multiorgan and multiliniage engrafment by a single BM-derived stem cell while the other reported that in their hands no such transdifferentiation could be observed (see first full paragraph in the left column on page 549). These arguments further enforce that the art of transdifferentiation of one bone marrow derived stem cell into multiple organs is controversial and unpredictable. It is noted that the specification as instantly filed does not provide any guidance or evidence that one stem cell (from adult bone marrow) could differentiated into adipocyte, cardiomyocyte, liver cell etc. as claimed. It is noted that applicants' group has published several articles (for example, Makino et al. J clinical Investigation 103:697- 705, 1999; Fukuda K. Bone Marrow Transplantation 32:S25-S27, 2003) however none of these articles disclose that a bone marrow stem cell that differentiates into a cardiomyocyte could differentiate into any other cell. Therefore, even four years after the time of the invention, the status of a multipotent stem cell that could differentiate into a cardiomyocyte, skeletal muscle, liver cell, an adipocyte, an osteoblast and a vascular endothelial cell was unpredictable and the specification has not provided any guidance or evidence that

an artisan of skill could isolate such a cell and differentiate into these recited cell types which functioned as the recited cell type.

In view of the unpredictability of the art as evidenced by the art of record and lack of guidance and working examples, an artisan of skill would have required extensive experimentation to practice the claimed invention as recited commensurate with the full scope of the claims and in spite of the high skill of an artisan working in the art, such experimentation would have been undue due to the unpredictability of the state of the art. Therefore, limiting the scope of the claimed invention to (i) an isolated mouse stem cells isolated from an adult mouse bone marrow, wherein said mouse stem cell differentiates into a cadiomyocyte and wherein said stem cell when transplanted in a mouse differentiates into cardiomyocyte or wherein said stem cell when transplanted into a mouse blastocyst differentiates into a cardiomyocyte, is proper.

Claim 40 recites the cells based on a particular process that is differentiation into a cardiomyocyte or a blood vessel when transplanted into a heart. However, the specification is not enabling for a heart transplantation as discussed below.

Claimed invention is drawn to a method of regenerating a heart damage by using a cell that can differentiate into a cardiomyocyte and an agent for cardiac regeneration.

The specification as filed is not enabling for a method of regenerating heart damage in a heart disease because the art of treatment using a pluripotent stem cell is unpredictable as evidence by the art of record discussed below and the specification does not provide sufficient guidance as to how an artisan of skill would have practiced the claimed invention without undue experimentation.

It is noted that at the time of the invention, the art of using stem cells to treat any condition other than that of hematopoietic cells was not routine and is not routine even today. There is no evidence in the art or in the specification that using any cell that can differentiate into cardiomyocyte one can treat a disease. Most importantly, a cell that is pluripotent when introduced in a patient will differentiate in every type of tissue it can differentiate into and therefore, the resultant cells will form a teratoma (see Klug et al (Journal of Clinical Investigation. 98:216-224,

1996) second paragraph in the right column on page 216). Furthermore, Klug et al noted: "while it remains to be established if any form of cellular engraftment can effect myocardial repair (see reference 26 for a critical review), it is virtually certain that human fetal donor cariomyocytes can not be obtained in sufficient numbers for use in a clinical setting." Therefore, at the time of the invention, the treatment of disease with a cell that differentiated into cardiomyocytes and that resulted in treatment or myocardial repair was not established. In addition to this, transplantation of any allogeneic or xenogeneic cells for treating a heart disease was also not routine in the art and an artisan of skill would not have know as to whether allogeneic or xenogeneic cells would have survived in a patient. Additionally, there is no teaching how many cells would have been transplanted or administered for effecting treatment, how will the cells be administered to a patient, whether sufficient number of cells will reach the site of damage, whether the cells will differentiate into cardiomyocytes and whether the resultant cardiomyocytes will function as heart muscle cells and treat the damage, how would an agent be administered to a patient to ensure that sufficient agent would reach site of heart damage and would cause differentiation of the cells to only cardiomyocytes, not to neural cells or to hepatocytes or any other cell type.

Mayer et al (American Journal of Heart 134:577-586, 1997) noted about myocardial grafting:

"If cells within the heart are induced to proliferate, it would be imperative to turn off replication after a sufficient level of repopulation. Uncontrolled proliferation in situ or metastasis from dividing or grafted cells would be unacceptable. Augmenting cardiomyocyte numbers is necessary but not sufficient for the goal of increasing effective myocardial mass; the new myocytes must be functional with properties that include contractile phenotype and integration into the electrical and mechanical activity of the heart. If they do not work in conjunction with existing myocytes, they may create a nonfunctional scar, predisposing to ventricular modeling, dilation, worsening heart failure, and arrhythmias."

There is no evidence of record that the cells transplanted as claimed will function as heart cells in terms of contractile phenotype and integration into

electrical and mechanical activity of the heart and that they will work in conjuction with the existing myocytes. It is reiterated that the art of cell transplantation was not routine in the art for treating heart disease by administering any stem cell to a patient along with an agent that causes differentiation of these cells in to cardiomyocytes and the specification as filed does not provide sufficient guidance for an artisan to address the enablement issues raised above and therefore an artisan of skill would have required extensive experimentation to figure out and address the issues raised above. Such experimentation would have been undue because neither the art nor the specification at the time of the invention taught how to perform such experimentation.

It is noted that claims 45-46 also recite a cell based on a functionality, i.e. differentiation into a nerve cell or a hepatic cell after transplantation, however, these inventions are not enabled for reasons of record discussed. It is emphasized that as discussed above, differentiation of a multipotent cell into a hepatic cell or a nerve cell is not enabled, therefore, claims 45-46 that recite transplantation are not enabled.

7. Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The application discloses multipotential stem cell FERM BP-7043 that is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is noted that this is a specific mouse stem cell line recited in claim 25. It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public.

Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

8. Claims 29, 30 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed invention (claim 29) is directed to a cells that are exposed to any factor that is expressed in a cardiogenesis region of a fetur or a factor which acts on differentiation into cardiomyocyte in a cardiogenesis stage. Claim 30 is directed to any cytokine, any adhesion molecule, any vitamin, any transcription factor, any DNA demethylation agent and any extracellular matric. Claim 42 recites an activator of a nuclear receptor, PPAR-g.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been

described by their complete structure. When the claims are analyzed in light of the specification, instant invention recites several distinct genera, any factor that is expressed in a cardiogenesis region or a factor, which acts on differentiation into cardiomyocyte in a cardiogenesis stage. However, the specification does not teach what is the complete structure of any species of the genus. Except for reciting that the factor is expressed in a cardiogenesis region or stage, the specification does not teach what would be the structure of a species of the genus.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification does not teach any identifying characteristic except that it is expressed euring cardiogenesis or in a cardiogenesis stage. Regarding claim 30, it is noted that while the several vitamins, cytokines, adhesion molecules, transcription factor and extracellular matrix are known in the art, the specification does not teach what are the identifying characteristics of a vitamins, cytokines, adhesion molecules, transcription factor, DNA demethylation agent, activator of a nuclear receptor and extracellular matrix, that would cause them to effect differentiation of a multipotent marrow stem cell into a cardiomyocyte. It is noted that all these factors or agents vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of these subgenera themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenera.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of the modulators or agents at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-46 and 76-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite because it recites a broader limitation compared to the claim it is dependent on. Claim 1 recites a multipotential stem cell that can differentiation into each of a list of five different cell types, however claim 7 recites that the stem cell differentiates into any cell.

Claim 20 is indefinite because it recites that the precursor cell only cardiomyocyte although the base claim, claim 1 recites that the cell can differentiate into any of a list of five cells.

Claim 45 is indefinite because it is unclear as to what is a "nervous cell."

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Klug et al (Genetically selected cardiomyocytes from differentiating embryonic stem cells form stable intracardiac grafts. Journal of Clinical Investigation. 98:216-224, 1996) for reasons of record set forth in the previous office action of 6-20-03.

13. Claims 1-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Juttermann et al (Proc. Natl. Acad. Sci. USA. 91:11797-11801, 1991) for reasons of record set forth in the previous office action of 6-20-03.

14. for reasons of record set forth in the previous office action of 6-20-03Claims 1-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Pinney et al (Environmental Health Perspectives 80:221-227, 1989) for reasons of record set forth in the previous office action of 6-20-03.

15. Claims 1-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Shi et al (Blood 92:362-367, 1998)) for reasons of record set forth in the previous office action of 6-20-03.

16. Claims 1-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Young et al (Proceedings of the Society of Experimental Biology and Medicine. 221:63-71, 1999)).

17. Claims 1-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Makino et al (Journal of Clinical Investigation. 103:697-705, 1999) for reasons of record set forth in the previous office action of 6-20-03.

It is noted that all the 102 rejections are maintained for reasons of record because the invention as claimed only requires the cells to differentiate into different cells. While none of the references teaches that one cell differentiates into all the five different cell types recited, the claimed invention does not recite any other identifying feature and the applicants have not provided any evidence as to why the cells known in the art could not differentiate into any of the cells recited.

18. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-

0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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